IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of SCHLINGENSIEPEN, et al.	Confirmation No: 4668
Application No.: 10/591,048	Docket No.: 4052-3
Examiner: Louis WOLLENBERGER	
Filed: March 28, 2007	Group Art Unit: 1635
For: PHARMACEUTICAL COMPOSITION	

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

I, Dr. Karl-Hermann Schlingensiepen, declare as follows:

1. I am a co-inventor in patent application 10/591,048 entitled "PHARMACEUTICAL COMPOSITION." I am currently holding the position as CEO of Antisense Pharma GmbH, Regensburg.

2. I hold a MD and PhD in Medicine from the University of Göttingen. The work for my PhD was performed mainly at Cambridge University, UK and at the Max-Planck-Institute in Göttingen, as described in more detail in my curriculum vitae (c.v.) appended hereto. Since 1990, I have worked regularly in the field of TGF-beta and oncology. I have authored and co-authored about xx_67 (see attached list)___ publications regarding the same.

3. I have reviewed the Office Action dated July 15, 2010, and the prior art

references cited therein.

4. I have reviewed the following independent claims as amended in the Amendment filed herewith. These claims are copied below and appear in italics:

Claim 23 (Currently Amended): A method for inhibiting the formation of metastases in cancer treatment in a subject comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 ~~to a subject, wherein said at least one oligonucleotide inhibits the formation of metastases in said subject.~~

Claim 30 (Currently Amended): A method for cancer treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one TGF-beta2 antisense oligonucleotide inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of: prostate cancer, ~~bladder carcinoma, colon cancer, endometrial cancer, hepatocellular carcinoma, leukemia, lymphoma, melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer,~~ and pancreatic cancer ~~or is selected from the group of melanoma, renal cancer, leukaemia, lymphoma, osteosarcoma, mesothelioma, myeloma multiple and bladder cancer~~.

Claim 44 (Currently Amended): A method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer ~~melanoma, bladder cancer, endometrial cancer, esophageal cancer, hepatocellular cancer, non-small-cell lung~~

~~cancer, ovarian cancer, osteosarcoma, mesothelioma, renal cancer, myeloma multiple, pancreas carcinoma, leukaemia, lymphoma and soft tissue cancer.~~

5. U.S. Patent No. 6,455,689 to Schlingensiepen *et al.* ("Schlingensiepen II"), U.S. Patent No. 6,153,388 to Reintgen *et al.* ("Reintgen"), U.S. Patent No. 5,550,316 to Mintz ("Mintz"), U.S. Patent No. 4,999,339 to Paradise *et al.* ("Paradise"), U.S. Patent No. 5,843,974 to Swift ("Swift"), U.S. Patent No. 6,787,161 to Aylward ("Aylward"), U.S. Patent No. 5,610,280 to Brandt *et al.* ("Brandt"), and U.S. Patent No. 5,369,527 to McCracken ("McCracken"), U.S. Patent No. 6,120,763 to Fakhrai *et al.* ("Fakhrai I"), U.S. Patent Applic. Publ. No. 2004/0006030 to Monia *et al.* ("Monia"); and Am J. Pathol. 145(1):97-104 by Reed *et al.* ("Reed") were determined by the examiner to render the claimed invention obvious. According to the examiner:

> Accordingly, it would have been prima facie obvious at the time of invention to administer any of the anti-TGF-β oligonucleotides disclosed by Schlingensiepen et al. to a subject having melanoma with the reasonable expectation any of the oligonucleotides could effectively treat a melanoma (i.e., skin carcinogenesis) in which TGF-β was involved, as taught by Schlingensiepen et al. In treating melanoma with any of the Schlingensiepen et al. antisense oligonucleotide compounds the practitioner would necessarily obtain all biological effects inherent to the compound, including those recited by the claims, such as inhibition of metastasis. A compound and its properties are inseparable. As evidenced claims 26, 27, 33 and 41 of the instant application, the antisense oligonucleotide of SEQ ID NO:30, and therefore of SEQ ID NO:72, is an oligonucleotide that inhibits the formation of metastases and production of TGF-beta2. As evidenced by claims 28 and 29, which recite the method of claim 23 for treating esophageal and neurofibroma cancer, the administration of an oligonucleotide within the scope of claim 23, such as that comprising SEQ ID NO:72 (SEQ ID NO:30), will treat esophageal and neurofibroma cancers and inhibit the formation of metastases in such cancers. As evidenced by page 1, line 13, of the specification, TGF-β is in fact a protein whose synthesis is involved in metastasis.

U.S. Patent Applic. Pub. No. 2007/0196269 to Schlingensiepen *et al.* ("Schlingensiepen III"). U.S. Patent Applic. Pub. No. 2008/0214483 to

Schlingensiepen *et al.* ("Schlingensiepen IV"), Schlingensiepen II, Reinigen, Mintz, Paradise, Swift, Aylward, Brandt, McCracken, Fakhrai I, Monia, and Reed were determined by the examiner to render the claimed invention obvious. According to the examiner:

> Schlingensiepen et al. (US 2007/0196269) and Schlingensiepen et al. (US 2008/0214483) each disclosed antisense oligonucleotides and methods of use thereof within the scope of the instant claims for inhibiting TGF-β2 expression and treating skin carcinogenesis in a subject.
>
> Prior art references 1-11 are relied on for the reasons given above in the rejection of claims 28-33, 39-42 and 44 under 35 USC 103. As a whole the prior art reasonably suggested inhibiting the expression/production of TGF-β2 using antisense oligonucleotides to treat various forms of cancer, including melanoma, as implied by Schlingensiepen et al. in each of the applications above.
>
> Accordingly, the instant methods would have been prima facie obvious at the time.

Monia, Fakhrai I and U.S. Patent No. 7,101,843 to Fakhrai *et al.* ("Fakhrai II") were determined by the examiner to render the claimed invention obvious. According to the examiner:

> One of skill would immediately have recognized that the antisense oligonucleotide that inhibits TGF-β2 is the active agent responsible for the cancer treatment effect, and that the means by which the antisense is introduced or delivered is simply an expedient and a matter or design choice to maximize and sustain antisense-mediated inhibition of the target gene. Accordingly, one of skill would reasonably have expected that any effective means known in the art for delivering an antisense oligonucleotide into a subject in an amount effect to reduce TGF-β2 production as required for cancer treatment would produce substantially the same effect as that disclosed by Fakhrai et al., given that Monia et al. disclosed and recommended numerous such routes by which to deliver an oligonucleotide.

> All effects inherent to the use of antisense oligonucleotides that inhibit TGF-β2, including those recited in the instant claims, such as inhibition of metastasis formation, would necessarily be obtained by the administration of such oligonucleotides, since a compound and its properties are inseparable, and since, as evidenced by instant claim 25, the inhibition of TGF-β2 inhibits formation of metastases (MPEP 2112).

I respectfully disagree with these determinations for the reasons explained below.

6. I wish to emphasize one of the differences between the teachings of the cited references and what is presently claimed, i.e., that metastases and primary tumors often substantially differ in their gene expression and thus in their reaction to inhibitors. The methods described in the cited prior art documents concern the application of TGF-beta 2 antisense oligonucleotides to treat primary tumors, while the present claims are directed to inhibiting the formation of cancer metastases. Therefore, the combined teachings of these references are not sufficient to render the claimed methods obvious. Based on the combinations of references, the person skilled in the art could not have expected that a treatment with TGF-beta2 antisense oligonucleotides might be successful in inhibiting the formation of metastases. To provide evidence in support of these assertions, several abstracts and scientific papers discussing the differences between primary tumors and matched metastases are filed herewith accompanied by a Supplemental Information Disclosure Statement. Of particular interest is Smith et al. 2005, which compares the gene expression of metastatic melanomas to non-metastatic melanomas. Also of particular interest is the abstract of Ujhazy V and Stracky J describing different drug sensitivity in primary tumors and metastases.

7. Subsequent to the filing of the present application, I generated additional data demonstrating the effect of specific TGF-beta antisense oligonucleotides on cell migration, and the inhibition of formation of metastases. This data is described in my manuscript entitled "TGF-β2 Gene Silencing with Trabedersen (AP 12009) in Pancreatic

Cancer" filed herewith. The additional experimentation included the results of a spheroid migration assay (see FIG. 4 of my manuscript filed herewith), which show that a TGF-beta2 antibody is not effective in inhibiting the migration of human pancreatic cancer cells, i.e., in inhibiting the formation of metastases, which starts with cell migration, in comparison to a TGF-beta2 antisense oligonucleotide according to the present invention. These results confirm that the binding of an antibody to a target for example a cancer cell (for detection), and thus, also the binding of other molecules, like oligonucleotides does not necessarily result in inhibiting cell migration, and thus, in inhibiting the formation of metastasis. This would be an inaccurate extrapolation to make. Thus, combining Reintgen, which is solely directed to a method of determining the spread of metastatic melanoma by detection using optical means, with Schlingemiepen II (in combination with all other cited references), would not result in the presently claimed invention, and would not suggest to a person skilled in the art to inhibit the formation of metastases in cancer treatment in a subject by administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48. A person of skill in the art, considering all of the cited references in combination, would at the most select one of the prior art oligonucleotide sequences for the *detection* of metastatic melanoma.

8. I further state that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date

Dr. Karl-Hermann Schlingensiepen